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13. ABSTRACT *(Maximum 200 Words)*

The goals of the Advanced Cancer Detection Center include the discovery of molecular and genetic markers of cancer risk, the identification of individuals at high risk for cancer through screening and the testing of methods to prevent cancer. The projects included in this report are:

- Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers (PI: Tockman)
- Development of the Moffitt Cancer Network (PI: Krischer)
- The Tampa Bay Ovarian Cancer Study (PI: Sutphen)

Each of these projects is presented as a complete study in the attached materials.

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INTRODUCTION:

The **Advanced Cancer Detection Center** (ACDC) of the H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida received initial funding in October 1997. The creation of the Center followed a proposal that was developed in response to legislative language accompanying an appropriation in the Department of Defense budget that appeared in the September 28, 1996, Congressional Record:

"$3,500,000 is available only for the establishment of an advanced cancer detection center for military personnel, dependents, and retired service members, using a network that is in close geographic proximity and includes the following: a military hospital, a regional TRICARE provider, a Department of Veterans Affairs hospital or hospitals, and a medical facility with a focused cancer center that meets the National Cancer Institute eligibility requirements, with respect to research funding. The conferees would expect this center to conduct coordinated screening for cancer detection and treatment, to train military cancer specialists, and to develop improved cancer detection equipment and technology."

The ACDC at the H. Lee Moffitt Cancer Center and Research Institute has addressed these goals through studies that target the discovery of molecular and genetic markers of cancer risk, the identification of individuals at high risk for cancer through screening, and the testing of methods to prevent cancer. In addition, the ACDC created and supported education programs to provide increased cancer awareness, provide screening services, and has established working collaborations with the nearby James A. Haley VA Medical Center, the Bay Pines VA Medical Center and the MacDill Air Force Base Hospital.

The Advanced Cancer Detection Center supports research and demonstration projects that further its mission. An internal peer group and an external scientific advisory committee review each project for scientific merit. Preference is given to projects that have potential to lead to independent peer reviewed funding. During the current grant period, the ACDC supported three cancer prevention and control research protocols. The supported studies are:

Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers (Cohort Study),

The Moffitt Cancer Network as a Telemedicine and Teleconferencing Educational Tool for Health Care Providers (Network),

The Tampa Bay Ovarian Cancer Study (TBOCS),

In November, 2000, both the internal and external scientific advisory committees met to consider the progress of the ACDC and to review and recommend new projects for funding. In this review, four additional projects were selected:

Epoxide Hydrolase Genetic Polymorphisms and Their Functional Significance.
Automated Quantified Screening for Melanoma.

Breast Cancer Screening in High-Risk Women: Comparison of Magnetic Resonance Imaging (MRI) with Mammography.
Adaptive Computer Assisted Diagnosis (CAD) Method for Lung Nodule Early Detection.

These studies were to be supported by FY00 and FY01 funding which was appropriated at the level of $3.5 million for each year. On September 20, 2001 the U.S. Army Medical Research and Material Command, (MRMC) Ft. Detrick, MD awarded the ACDC $6,004,000.00. According to the agency, this contract fully obligates the FY00 ($3.5M) and FY 01 ($3.5M) money directed to the ACDC by Congress. The remaining $996,000.00 (14.2%) is being withheld by the agency for "overhead expenses." The delay in the obligation of these funds was attributed to a complex "RCQ" (Regulatory Compliance and Quality) approval process by the agency over "human use" issues such as human genetics. As a result, funding for these projects was shifted to DAMD 170120056. Progress reports on these studies are reported separately under this new award made to continue the ACDC. Indeed, only the Cohort, Network and TBOCS studies will receive continued funding from this award in FY02. Final reports, progress reports, and publications are being readied on the remaining studies, as appropriate, or continuation funding is being developed under other mechanisms.

BODY:

Overview: The H. Lee Cancer Moffitt Center & Research Institute includes a free standing patient care facility with a large inpatient and outpatient capacity, a major research institute consisting of more than 130 scientific members, a free standing Lifetime Cancer Screening Center and a wide array of outreach and educational activities for the general public and select underserved populations. Moffitt Cancer Center's location at the convergence of the University of South Florida's Health Sciences Center and the main campus sets the stage for its conceptual commitment to interdisciplinary approaches to research and patient care. Moreover, it allows the Center to enjoy all intellectual advantages of a matrix center while remaining operationally freestanding. After 14 years, the Cancer Center's mission remains totally focused on "contributing to the prevention and cure of cancer."

The Cancer Center was created by the Florida Legislature in the early 1980s to meet a clear and compelling need to respond to Florida's "cancer epidemic." Building a major cancer research and treatment center at the University of South Florida in Tampa was largely the vision of H. Lee Moffitt, a state legislator who served as Speaker of the Florida House of Representatives from 1982-84. Construction of the original, 380,000 square foot hospital facility was funded with $70 million from the state's cigarette tax, allowing the Center to open in 1986.

The initial phase of the Cancer Center's strategic plan called for a rapid and substantial deployment of its clinical, financial, and philanthropic resources to develop a true scientific center of excellence. The Center recruited Dr. John C. Ruckdeschel as the Cancer Center's first director in late 1991. In 1992, he began fulfilling that strategic plan,

a process that culminated in the awarding of a Cancer Center Support Grant (CCSG) five years later.

The strategic plan's second phase continues the focus on scientific and clinical growth, with a commitment to increase research facilities by over 200,000 sq.ft., and to prepare to accommodate twice as many patients by 2009. In 1998, the state legislature committed an additional $100 million to finance the construction needed to meet these goals.

In August, 2002, Dr. William Dalton was recruited to become the Cancer Center Director replacing Dr. Jack Ruckdeschel. Dr. Dalton was the Dean of the College of Medicine at the University of Arizona and previously was the Associate Center Director for Clinical Investigations at the Moffitt Cancer Center for five years. Thus, Dr. Dalton brings to his new role considerable experience in the operations of the Cancer Center and an in-depth background in the development of the Cancer Center's scientific agenda.

Today, the Cancer Center's membership numbers 150 scientists and clinicians who are USF faculty. More than 94 members-in-residence are housed and supported in the Center's facilities and work under the terms of the USF/Moffitt affiliation and faculty support agreements. Other members are based in University departments. The Cancer Center's 1,500 employees support the work of the physicians and scientists. The Center has annual operating revenues of over $130 million yearly, including an $11 million annual appropriation from the State of Florida, research grants totaling more than $36 million overall (direct), philanthropic donations, and institutional commitment from the University of South Florida in the form of faculty salaries and a portion of clinical practice revenues.

The Cancer Center currently supports four scientific programs:

Program	Leader	Members	Funding (Direct)
Molecular Oncology	Richard Jove, Ph.D.	21	$ 5,529,000
Immunology	Julie Djeu, Ph.D.	14	$ 2,542,000
Clinical Investigations	William Dalton, Ph.D., M.D.	58	$ 12,712,000
Cancer Control	Jeffrey Krischer, Ph.D.	39	$ 9,021,000
Non-aligned members & institutional grants	N/A	5	$ 6,581,000

The DoD funded Advanced Cancer Detection Center is administratively located with the Cancer Control Research Program. The overall goals of the Cancer Control Research Program remain focused on the reduction of the burden of cancer on individuals and society. The goals of the Cancer Control Research Program are translated into specific focused scientific aims that can be summarized as the application of multidisciplinary research to:

Aim 1 Susceptibility	Identify markers that predict increased cancer susceptibility.
Aim 2 Prevention	Evaluate promising interventions directed at the prevention of cancer.
Aim 3 Early Detection	Develop and test new early detection strategies.
Aim 4 Health Outcomes	Evaluate interventions to improve the quality of life for cancer patients & their care-givers.

These aims are consistent with those of the Advanced Cancer Detection Center and the funding has been utilized to create an infrastructure to promote the goals of the Cancer Control Research Program by:

- Encouraging collaborative research
- Providing funding for studies that can lead to extramural peer-reviewed funding
- Providing core competencies to support Cancer Control investigators

In order to provide an appropriate mechanism to allocate and manage these funds, the Cancer Center created an administrative core, an internal scientific review committee, and an external advisory committee. The administrative core manages the resources and personnel, associated with the ACDC funding, and provides liaison with the Department of the Army and the regulatory bodies that oversee the research. The internal scientific review committee conducts a scientific review of the merits of proposed projects and their potential for peer-reviewed funding and makes funding recommendations. The external advisory committee reviews the organizational structure and scientific directions of the Advanced Cancer Detection Center and the progress made by the individual projects.

The membership of the internal scientific review committee changes as necessary to have adequate scientific expertise to evaluate proposals submitted to the ACDC. This year the members are:

Dr. Dmitry Goldgof, Associate Professor, Computer Science and Engineering, College of Engineering
Dr. Pamela Munster, Assistant Professor, Department of Interdisciplinary Oncology, College of Medicine
Dr. Santo Nicosia, Professor and Chair, Department of Pathology, College of Medicine
Dr. Robert Clark, Professor and Chair, Department of Radiology, College of Medicine
Dr. Jeffrey Krischer, ex officio, Professor, Department of Interdisciplinary Oncology, College of Medicine

Cancer Control science at the H. Lee Moffitt Cancer Center and Research Institute is greatly enhanced and facilitated by the development of infrastructure that provides access to shared resources, promotes collaboration and funds pilot projects. Over the last three years, the Cancer Control Program has established new infrastructure to meet these

needs. The funding of the Advanced Cancer Detection Center is one of three mechanisms by which this has occurred.

Advanced Cancer Detection Center

The Advanced Cancer Detection Center has become a significant component of the Moffitt Cancer Control Program infrastructure in that it provides a stimulus for research development and promotes inter and intra programmatic collaborations. The Advanced Cancer Detection Center supports pilot studies that can lead to peer-reviewed extramural funding. Projects supported by this mechanism follow a two-tiered scientific review process in which the science and the likelihood of peer-reviewed extramural funding are considered. In addition, priority is given to projects that foster inter and intra-programmatic collaborations.

Moffitt CCOP Research Base (PI:Krischer)

The H. Lee Moffitt Cancer Center received funding by the NCI in June 2000 to develop a research base as a mechanism for Community Clinical Oncology Programs to access cancer control clinical trials. NCI CCOPs and Moffitt affiliates are eligible to participate in the Moffitt CCOP Research Base. Membership is based on continued funding as an NCI CCOP with satisfactory performance measured by accrual and data quality.

The goals of the Moffitt CCOP Research Base are to:

- Develop cancer control trials of high scientific merit for implementation in the community setting.
- Provide community investigators an opportunity to participate in NCI-supported cancer control clinical trials.

The following CCOPs have, or are in the process of, establishing formal affiliations with the Moffitt CCOP research base:
Florida Pediatric CCOP, Tampa, FL
Merit Care Hospital CCOP, Fargo, ND
Mount Sinai Medical Center CCOP, Miami, FL
South Texas Pediatric MBCCOP, San Antonio, TX
Baptist Center Research Institute CCOP, Memphis, TN
Cancer Research for the Ozarks CCOP, Springfield, MO
Columbus CCOP, Columbus, OH
Greater Phoenix CCOP, Phoenix, AZ
North Shore University Hospital CCOP, Manhassett, NY
NorthWest CCOP, Boise, ID
Southern Nevada Cancer Research Foundation CCOP, Las Vegas, NV

The Moffitt CCOP Research Base is now staffed and cancer control protocols and concepts are being initiated. Several of the clinical studies are the result of pilot development funded by ACDC projects:

A Clinical Trial of the Action of Isoflavones in Breast Neoplasia: Administration Prior to Mastectomy or Lumpectomy -- A Pilot Study — Protocol

The Specific Role of Isoflavones in Reducing Prostate Cancer Risk	Protocol
A Randomized Pilot Clinical Trial of the Action of Isoflavones and Lycopene in Localized Prostate Cancer:Administration Prior to Radical Prostatectomy.	Protocol
Megestrol Acetate (Megace) as an Appetite Stimulant in Children	Protocol
Cancer Genetic Counseling and Testing by Telemedicine in Community Settings	Concept
Methylphenidate for the Treatment of Cognitive Difficulties in Patients with Primary Brain Tumors: A Double-Blinded, Placebo-Controlled, Parallel Group Study	Concept
Stress Management Training for Patients Undergoing Radiotherapy	Protocol

Lifetime Cancer Screening and Diagnostic Center

The Lifetime Cancer Screening and Diagnostic Center was administratively realigned during 2001 to be integral to the Cancer Control Program, with the objective of increasing opportunities for cancer control clinical research to be conducted at that site. Now more than a dozen cancer control studies are based at LCS. Also, plans have now been made to consolidate cancer control researchers into the Moffitt Research Center as clinics become relocated with the opening of new clinical space. This will provide enhanced opportunities for collaboration as well as improved access to clinical space in which to conduct cancer control studies. The ACDC supported studies in cancer genetics, screening for breast cancer, and screening for lung cancer are all conducted at this site.

(1) KEY RESEARCH ACCOMPLISHMENTS:

The material that follows in this section summarizes the key research accomplishments associated with each project and task outlined in the appropriate approved Statement of Work for ACDC approved projects. **A full description of the projects and their progress is appended.**

Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers, Genetic Analysis of Familial Prostate Cancer

- Developed an infrastructure to identify, accrue, screen and follow a non-diseased community-dwelling population at high risk for lung cancer.

- Developed procedures for collection and preservation of sputum specimens for new (DNA, RNA, protein and morphologic) markers of pre-neoplasia.

- Developed an archive of airways cytologic specimens suitable for evaluation of new (DNA, RNA, protein and morphologic) markers of pre-neoplasia.

- Developed an archive of white blood cells suitable to provide individual control specimens for DNA and RNA

- Developed a potency assay for MoAb 703D4 immunodetection of hnRNP A2/B1 protein expression.

- Identified a panel of 15 LOH markers for sputum lung cancer screening which identifies 84% of lung tumors.

- Completed the initial lung cancer screening of 1151 middle-aged current and former smokers. Approximately 50% are found in stage I, a 3-fold greater frequency of stage I detection compared to the current clinical standard of no screening as reported by the Florida Cancer Registry.

Development of the Moffitt Cancer Network

- The Moffitt Cancer Network is available to users and can be found at
  http://network.moffitt.usf.edu

- The MCN currently has 496 presentations in its library, increasing at a rate of 16 presentations per month on average. Additionally, 13 conferences sponsored by USF and Moffitt are also currently available online.

- All approved Grand Rounds presentations have been taped by the Moffitt Multimedia Education Resources Center (MERC) for over two year preceding this report. The video was previously captured on digital DVCAM 94 minute tapes. Currently we are running in a tape-less environment.

- Since many of the presenters use only 35mm slide for their presentations, a process of creating final production audio/video Real media for streaming via TCP/IP has been developed. This process requires post-production labor and requires the best of the video's individual frames to be captured a second time to recreate higher quality computer images. MCN has made significant progress in this area and as of June 2000 has begun using presenter's PowerPoint files when ever possible to bypass the second image rendering process. This has reduced labor time from 3.5 days to about 5 hours, while increasing image quality noticeably. This labor savings is not realized when presenters are using 35mm film only. This methodology was modified to capture slides, overheads and computer screens digitally without a camera. The new methodology has reduced post-production time to virtually nothing. This allows us to concentrate on acquisition of new material.

In addition to pre-presentation file acquisition, MCN has begun the development of a presenter packet. When finished, this packet will inform presenters to repeat important questions asked at the end of events like Grand Rounds and these will be added to the content to be available to medical professionals at the MCN website.

- National oncology conferences have been taped and included in the MCN website database.

- Conferences have been subdivided into their respective presentations and are categorized searchable as well as searchable using the website database Access Jet engine. All conferences are pre-qualified for their ability to become online educational materials by the University of South Florida College of Medicine and, more recently, the University of South Florida College of Nursing.

- MCN began simultaneous live streaming and archiving in late 2001. This process greatly reduces postproduction time while increasing access to live events.

- MCN has completed the move to camera-less and tape-less acquisition of presentations using a host of digital equipment.

The Tampa Bay Ovarian Cancer Study

- Aim 1: We are successfully collecting data regarding health behaviors and risk factors from all participants via questionnaire instruments and study interview.
- Aim 2: We are successfully collecting detailed cancer family history from all participants via questionnaire instruments and study interview.
- Aim 3: We have established a successful mechanism to obtain medical records and tumor tissue in order to compare tumor characteristics between mutation-associated cases and non-mutation controls.
- Aim 4: We have established a successful follow-up mechanism to obtain data regarding differences in response to treatment and survival between mutation-associated cases and non-mutation controls.
- Aim 5: We are implementing additional strategies to achieve 80% participation of eligible cases and anticipate success by summer 2002.

(2) REPORTABLE OUTCOMES:

Manuscripts, abstracts, presentations:

Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers

Publications Related to this Study:

1. Baker SG and **Tockman MS**. *Evaluating Serial Observations of Precancerous Lesions For Further Study as a Trigger For Early Intervention.* Statistics in Medicine. In Press.

2. Toyooka S, Fukuyama Y, Wistuba II, **Tockman MS**, Minna JD, Gazdar AF. *Differential Expression of FEZ1/LZTS1 Gene in Lung Cancers and Their Cell Cultures.* Clinical Cancer Research. 2002 July; Vol 8 2292-2297.

3. Chirikos T, Hazelton T, **Tockman MS**, and Clark R. *Screening for Lung Cancer with CT: A Preliminary Cost-Effective Analysis.* CHEST 2002; May 121:1507-14.

4. Zhou J, Nong L, Wloch M, Cantor A, Mulshine JL, **Tockman MS**. *Expression of early lung cancer detection marker: hnRNP A2/B1 and its relation to microsatellite alteration in non-small cell lung cancer.* Lung Cancer. 2001; Dec 32(3):341-50.

5. Mulshine JL, De Luca LM, Dedrick RL, **Tockman MS**, Webster R, Placke ME. *Considerations in developing successful, population-based molecular screening lung cancer.* Cancer. Dec 1, 2000; 89(11 Suppl):2465-7. Review.

6. **Tockman MS**, Mulshine JL. *The early detection of occult lung cancer.* Chest Surg Clin N Am. Nov 2000; 10(4):737-49.

7. **Tockman MS**. *Advances in Sputum Analysis for Screening and Early Detection of Lung Cancer.* Cancer Control, Journal of the Moffitt Cancer Center. January/February 2000, Vol. 7, No. 1:19-24.

8. Kennedy TC, Proudfoot SP, Piantadosi S, Wu L, Saccomanno G, Petty TL, **Tockman MS**. *Efficacy of Two Sputum Collection Techniques in Patients with Air Flow Obstruction.* ACTA Cytologica. July-August 1999; Vol. 43, No. 4:630-636.

Abstracts Related to this Study:

1. Zhukov TA, Johanson R, **Tockman MS**. *Discovery of distinct protein profiling specific for lung tumors and pre-malignant lung lesions by SELDI mass spectrometry.* Proceedings of the AACR, Volume 43, March 2002. Page 36, #184.

2. Zhukov TA, Erozan YS, **Tockman MS.** *Sentinel Cell for Lung Cancer.* 14th International Congress of Cytology, RAI Congress Centre, Amsterdam, The Netherlands. May 2001.

3. Mulshine JL, **Tockman MS**, Martinez A, Man Y-G, Montuennga L, Hong SH. *Application of Molecular Biology for Early Detection of Lung Cancer.* 1999.

4. Zhou J, Nong L, Wloch M, Zhukov TA, and **Tockman MS**. *Expression of Early Lung Cancer Detection Marker: hnRNP a2/b1 and its Relation to Microsatellite Instability in Non-Small Cell Lung Cancer*. Proc. AACR, April 1999, 40:140-141

5. Truncale T, Zhou J, Zhukov TA, Muñoz-Antonia T, Antonia S, Muro-Cacho C, **Tockman MS**. *Evaluation of TGF-ß II Receptor Expression (TßR-II) and a Common Signaling Mediator SMAD4 in NSCLC*. Proc. AACR, April 1999, 40:337.

6. Falestiny MN, Cardona JJ, Zhou J, Zhukov TA, Nong L, Solomon DA, **Tockman MS**. *Transforming Growth Factor ß Type II Receptor Expression in Non-Small Cell Lung Cancer, Viral Transformed Bronchial Cells and Normal Bronchial Epithelial Cells: A Comparative Study*. Chest (Suppl); November 1998.

7. **Tockman MS**, Saccomanno G, Michels R, Zhukov TA, Erozan Y, and Gupta P. *Sentinel Cell for Lung Cancer*. 6th SPORE Investigator's Workshop; July 1998.

Presentations Related to this Study:

December 8-10, 1998	International Conference on Prevention and Early Diagnosis of Lung Cancer, Johns Hopkins Lung Project and Immunocytochemical Screening for Lung Cancer. University of Varese and University of Massachusetts Medical School, Varese, Italy.
February 12, 1999	ALCASE Workshop – Lung Cancer: A Revolution in Care, Technology in Early Diagnosis of Lung Cancer. Embassy Suites, Tampa, Florida
April 26, 1999	1999 ALA/ATS International Conference Program, Early Sputum Marker for Lung Cancer (hnRNP). San Diego Convention Center, San Diego, California
April 30, 1999	Pharmacology Seminar Program, Detection and Immunostaining of the Lung Cancer Sentinel Cell. University of Pittsburgh, Pennsylvania.
September 13, 1999	Advanced Cancer Detection Center, External Advisory Committee. Moffitt Cancer Center, Tampa, Florida
September 30 to October 3, 1999	The First International Conference on Screening for Lung Cancer, Cornell University, New York
October 9-13, 1999	Annual Congress of the European Respiratory Society, Dysregulation of the Cell Cycle in Lung Cancer. Madrid, Spain
October 15-16, 1999	Molecular Biomarkers Workshop, Roy Castle Lung Cancer Foundation, Liverpool, England
October 26, 1999	Screening of Lung Cancer Conference, Gaithersburg, MD
October 31, 1999	7th Annual Scientific Assembly of the American Association of Bronchology, New horizons in cytological based early detection in lung cancer. Chicago, IL

February 9, 2000	International Symposium on Early Detection of Lung Cancer, Molecular Screening Program: Past, Present, and Future. Tel Aviv, Israel
February 27-29, 2000	International Agency for Research on Cancer, Use of Biomarkers in Chemoprevention of Cancer, Lung Cancer: Intermediate Effect Markers. Heidelberg, Germany
March 20, 2000	Cahan Lectureship at Memorial-Sloan Kettering, Molecular Screening for Lung Cancer. New York, NY
April 12, 2000	Early Detection Research Network Site Visit at H. Lee Moffitt Cancer Center & Research Institute, Organization of BeDLAM. Tampa, FL
June 16, 2000	Wayne State University Cancer Conference, Sputum in 2000: Hypothetical Advantages, Practical Limitations, and Novel Approaches, Detroit, MI
June 22, 2000	Reducing Lung Cancer Mortality: Actions for the New Millenium, Sputum Based Detection of Preinvasive Lung Cancer, Washington, DC
June 27, 2000	Roy Castle Lung Cancer Foundation and H. Lee Moffitt Cancer Center, Quest for the Cure, Lung Cancer Screening and Early Detection: Spiral CT Scanning and Molecular Markers, Tampa, FL
July 19, 2000	H. Lee Moffitt Cancer Center/USF Lung Cancer Conference, Epidemiology and Early Detection of Lung Cancer, Coeur d'Alene, ID
July 19, 2000	H. Lee Moffitt Cancer Center/USF Lung Cancer Conference, The Management of Pre-Clinical Lung Cancer, Coeur d'Alene, ID
September 12, 2000	IASLC 9th World Conference on Lung Cancer, Cellular Targeting in the Molecular Diagnosis of Lung Cancer, Tokyo, Japan
October 24, 2000	(1) 66th International Scientific Assembly of the ACCP, San Francisco, CA (2) ACCP Post Graduate Course, Screening and Early Detection of Lung Cancer (3) Meet the Professor, Sputum Detection of Early Lung Cancer: Hypothetical Advantages, Practical Limitations, and Novel Approaches
October 27, 2000	Cornell CT Conference, Sputum Detection of Early Lung Cancer: A Compliment to Helical CT, New York, NY
March 7-8, 2001	Lung Cancer Early Detection Workshop, National Cancer Institute/ American Cancer Society, "New Frontiers of Screening Science". Rockville, MD
March 24-25, 2001	Second Annual – A Practical Pulmonary Review for Primary Care Providers, University of South Florida/Department of Veterans Affairs, James Haley, "Early Recognition of Lung Cancer". St. Pete Beach, FL

June 20-22, 2001	Early Detection Research Network, National Institute of Health/National Cancer Institute, "Lung Cancer Screening Update" and "Industrial Partnership with EDRN", Washington, DC
June 26-July 2, 2001	Second International Lung Cancer Molecular Biomarkers Workshop "A European Strategy for Developing Lung Cancer Molecular and Clinical Diagnostics in High Risk Populations, Roy Castle Lung Cancer Foundation, "Sputum in 2001: Hypothetical Advantage Practical Limitations, and Novel Approaches" and "Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers" Liverpool, England
August 7-12, 2001	Third International Conference on Prevention & Early Detection of Lung Cancer, International Association for the Study of Lung Cancer, "Cellular Approaches to Lung Cancer Detection" and "Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers". Rejkjayik, Iceland
October 13-17, 2001	EDRN Scientific Workshop, Seattle, WA
October 26-29, 2001	Fifth International Conference on Screening for Lung Cancer, New York, NY
December 5-6, 2001	NCI Grant Review Meeting RFA CA-02008 Chemoprevention of Tobacco-related Cancers in Former Smokers: Preclinical Studies, Washington, DC
February 3-5, 2002	EDRN Steering Committee, Houston, TX
March 10-15, 2002	New Frontiers in Cancer Detection & Diagnosis (EDRN/ Gordon Research Conference), Ventura, CA
April 5-7, 2002	Sixth International Conference on Screening for Lung Cancer, Paris, France
June 13, 2002	NIH Women Tobacco & Cancer Steering Committee, Bethesda, MD
June 22, 2002	Great Cancer Roundup: Lung Cancer Screening & Prevention Conference, Los Angeles, CA
September 3-5, 2002	Sixth EDRN Steering Committee, Ann Arbor, MI
October 11-15, 2002	Molecular Targets in Cancer Therapy, St. Petersburg, FL
October 18-20, 2002	Seventh International Conference on Screening for Lung Cancer, New York, NY
October 28-30, 2002	First International Lung Cancer Conference, Beijing, China

The Tampa Bay Ovarian Cancer Study

Based on the epidemiologic design of the Tampa Bay Ovarian Cancer Study, funding was awarded by the American Cancer Society for a 3-year companion study to evaluate the role of biologically active lysophospholipids for their potential as biomarkers of ovarian cancer. Preliminary data is promising and shows that certain lysolipids appear to be elevated in the plasma of women with ovarian cancer compared with healthy controls. Based on this preliminary data, we have applied for an R01 to investigate the use of lysolipid measurement for detection of ovarian cancer in a population of women at increased risk of ovarian cancer, including first-degree relatives of women in TBOCS

(ovarian cancer patients). Our ongoing contact with women in TBOCS will facilitate the identification and enrollment of their female relatives at increased risk for enrollment in this important study, toward the development of an early detection test for ovarian cancer.

Based on data showing that gene mutations associated with Hereditary Non-Polyposis Colorectal Cancer (HNPCC) are the third leading cause of hereditary ovarian cancer (after BRCA1 and BRCA2), and the suggestion that ovarian cancer is a "sentinel cancer" in individuals with these gene mutations, funding for the investigation of HNPCC as a companion study of TBOCS has been funded.

Abstract Related to this Study

- Tuya Pal, Jeffery P. Krischer, Tricia Holtje, Judith A. Betts, Jenny Permuth Wey, James Fiorica, Edward Grendys, James LaPolla, Hector Arango, Katie Wakeley, Mitchell Hoffman, George Wilbanks, Santo Nicosia, **Rebecca Sutphen** and the Tampa Bay Ovarian Cancer Coalition. *Tampa Bay Ovarian Cancer Study – A Population-based Study of BRCA1/2 in Ovarian Cancer.* American Society of Human Genetics Annual Meeting, 2002

Development of the Moffitt Cancer Network

Abstracts Related to this Study:

- J Permuth-Wey, JA Betts, AB Cantor, JP Krischer, R Sutphen: Cancer Genetic Counseling and Testing by Telemedicine - Results of a Feasibility Study (Abstract). American Journal of Human Genetics (2002) 71(4): 343.

Presentations Related to this Study

- The Moffitt Cancer Network Vision, Jeffery Krischer, Ph.D. April 2001
- The Moffitt Cancer Network, Lessons Learned and New Directions, Matthew Clark, B.S. October 2001
- The Moffitt Cancer Network 2002, Matthew Clark, B.S. April 2002
- Keyword Indexing: Adding Value to the Moffitt Cancer Network [MCN] Web-based Education, Sue Felber, M.S., May 19, 2002 Medical Library Association Conference, Dallas TX
- No-latency video architecture, efficiency and a new tomorrow for on-line education, Matthew Clark, B.S. June 2002
- Keyword Indexing: Adding Value to the Moffitt Cancer Network [MCN] Web-based Education, Sue Felber, M.S.,June 19, 2002 Tech Topics, Moffitt
- Keyword Indexing: Adding Value to the Moffitt Cancer Network [MCN] Web-based Education, Sue Felber, M.S.,October 19, 2002 Southern Chapter, Medical Library Association
- Disseminating Library Instruction to the Desktop via the Web, Sue Felber, M.S.,October 19, 2002 Southern Chapter, Medical Library Association
- Telemedicine Today and Tomorrow, Matthew Clark, B.S. October 2002

- **Patents and licenses applied for and/or issued:**

  Development of the Moffitt Cancer Network

  A notice of disclosure has been filed with the USF office of patents in anticipation of the completion of a patent application.

- **Funding applied for based on work supported by this award:**

  Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers

  1. "The Biomarker Development Laboratory at Moffitt" (NCI-CA 84973, M. Tockman, PI, 1st year/Total award $413,720/$1,903,827).
  2. "Identification of the lung cancer epitope identified by the monoclonal antibody 703D4" (Cancer Research Foundation of America, M. Gruidl, PI, Total award $38,950)
  3. J. Park, PI, NCI-EDRN, Total award $98,000.

  The Tampa Bay Ovarian Cancer Study

  - Based on the epidemiologic design of the Tampa Bay Ovarian Cancer Study, funding was awarded by the American Cancer Society for a 3-year companion study to evaluate the role of biologically active lysophospholipids for their potential as biomarkers of ovarian cancer. Preliminary data is promising and shows that certain lysolipids appear to be elevated in the plasma of women with ovarian cancer compared with healthy controls. Based on this preliminary data, we have applied for an R01 to investigate the use of lysolipid measurement for detection of ovarian cancer in a population of women at increased risk of ovarian cancer, including first-degree relatives of women in TBOCS (ovarian cancer patients). Our ongoing contact with women in TBOCS will facilitate the identification and enrollment of their female relatives at increased risk for enrollment in this important study, toward the development of an early detection test for ovarian cancer.

  - Based on the promising preliminary results from our current investigations of lysolipids as biomarkers of ovarian cancer, we are also seeking funding from NCI for an investigation of these substances for their use as markers of recurrence of ovarian cancer, in a community-based investigation of ovarian cancer patients.

(3) CONCLUSIONS:

The Advanced Cancer Detection Center has been a great success. It has attracted quality research projects from among Cancer Center members, it has promoted inter and intra programmatic research and its projects have begun to lead to peer-reviewed extramural funding. Two of these studies (Selenium, DAMD 17-00-1-0062, and the Moffitt Cancer Network, DAMD 17-00-1-0055) received independent peer-reviewed funding from the Department of Defense in February, 2000. Based on the epidemiologic design of the

Tampa Bay Ovarian Cancer Study supported by this award, funding was awarded by the American Cancer Society for a 3-year companion study to evaluate the role of biologically active lysophospholipids for their potential as biomarkers of ovarian cancer. The study of markers of transformation in airways epithelial cells from a cohort of obstructed smokers and former smokers supported the establishment of the Biomarker Development Laboratory at Moffitt also funded by the National Cancer Institute, (PI: M. Tockman,). The Cohort Study is the only study in the nation that currently evaluates both molecular airways markers and helical CT examinations simultaneously in the prospective detection of lung cancer. Until the Cornell and Mayo studies begin their collection of sputum specimens, no other study addresses the relative merits of these apparently complementary techniques for lung cancer screening. This research question addresses the most common cause of cancer death and the only common cancer for which no screening is available. Finally, the archive of radiographs, sputum and blood cell specimens provides an infrastructure for other investigators at Moffitt and across the nation. The recent award to Dr. Jong Park of an NCI Early Detection Research Network grant was based on the availability of the Cohort archive.

The current funding period has been extended to permit the successful conclusion of projects that are still in the accrual or analysis phases. Manuscripts, presentations and grant proposals are under development to communicate the results of these efforts widely and to secure additional funding to pursue promising findings. The Moffitt Cancer Network is a functioning, stable educational forum and entering its evaluation phase. New funding has been put in place to continue the efforts of the Advanced Cancer Detection Center and to transform it into a DoD Center of Excellence to recognize its capability to identify and fund outstanding research from the entire Cancer Center.

(4) **REFERENCES:**

References pertinent to the individual projects are contained in the appended material.

Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers (DoD Cohort Study)

Principal Investigator: Melvyn Tockman, M.D., Ph.D.

I. Introduction

A. Lung Cancer Screening with Helical CT and hnRNP A2/B1

Two promising and practical screening techniques, computerized molecular analysis of airway cell markers (ACM) and helical computed tomography (CT), are now available to examine targeted populations for the earliest signs of lung cancer. This study will compare the accuracy (sensitivity and specificity) of these screening techniques as well as the stage distribution of lung cancer detected by these methods. We have now completed the accrual required for this study and are preparing to report the Moffitt prevalence experience with helical CT screening for lung cancer.

Henschke et al (Lancet, 1999 354:99-105) found that 10% of helical CT-detected noncalcified nodules from 2-5 mm through 21-45 mm contained a primary lung cancer. This is four times the sensitivity of a standard chest x-ray taken at the same time. Our preliminary data (Clin Cancer Res, 1997, 3:2237-46) showed that computerized immuno-detection of up-regulated hnRNP A2/B1 expression in sputum cells detected primary lung cancer in 37 of 45 (82%) cases. This is 8 times the sensitivity of standard sputum cytology obtained at the same time.

It is quite likely that the helical CT and ACM protein expression screening are complementary. The cell type distribution of the detected cancers suggests this. Lung cancer cell types infrequently detected by helical CT (squamous and small cell) may be detected by ACM. Evaluation of the extent to which these early lung cancer detection techniques are complementary could only be conducted in a one-arm prospective study such as this one, where every individual is screened by all techniques at the same examination.

B. Other Airway Cell Markers of Lung Cancer Evaluated with Cohort Specimens

In parallel, our NCI-EDRN Biomarker Developmental Laboratory at Moffitt (BeDLAM) grant supports the examination of other potential molecular markers on archived specimens from this Cohort trial. Several years ago with David Sidransky at Hopkins, we pioneered the use of microsatellite alterations as clonal markers in the detection of human cancer (Proc Natl Acad Sci USA 1994; 91:9871-75). We have found that microsatellite alteration and LOH on 3p is significantly associated with upregulation of hnRNP A2/B1 (Proc. AACR 1999; 40:140-1 Lung Cancer. 2001; Dec 32(3):341-50). Further, loss at 3p22, the site of gene for the Type II Transforming Growth Factor Beta Receptor is strongly associated with NSCLC (Clin Cancer Res. 2001 Jun;7(6):1618-26). Altered messenger RNA and proteins of the downstream tumor suppressor TGF-ß signaling pathway are of great interest in our laboratory (Clin Cancer Res. 2001 Jun;7(6):1618-26). BeDLAM funding also supports evaluation of the extent to which gene-specific promoter hypermethylation, detected in archived sputum cells, predicts the development of lung cancer. Therefore, we have developed a technique for preservation of sputum morphology and nucleic acids so that (DNA) promoter hypermethylation and microsatellite alterations as well as altered TGF-ß type II receptor message expression (RNA markers) may be examined in the sputum specimens collected in this study.

C. Ventilatory Obstruction (impaired spirometry) Enhances the Lung Cancer Risk of Cohort Participants
Age and cigarette smoking are not the only lung cancer risk factors considered in this study. We have shown that current and former smokers distinguished by airways obstruction are at 2-4 fold risk of developing lung cancer compared to non-obstructed smokers (Ann Int Med 1987:106:512-8). This result has been corroborated in the Multiple Risk Factor Intervention Trial, a randomized clinical trial for the primary prevention of coronary heart disease that enrolled 12,866 men. In that study, ventilatory function was a powerful predictor of lung cancer deaths, with rates that increased from 3.02 per 1,000 person-years in the lowest quintile of forced expiratory volume to 0.43 in the highest quintile (Am J Epidemiol. 1990 Aug;132(2):265-74). A similarly high lung cancer frequency among obstructed current and former smokers has been observed more recently among the participants in the Colorado Lung Cancer SPORE (Cancer Res. 1996 Oct 15;56(20):4673-8).

D. Former Smokers Remain at Risk of Lung Cancer and Could Benefit from Screening
The populations of greatest interest for lung cancer screening are the estimated 46 million former smokers in the United States who remain at risk despite smoking cessation. While cardiovascular risk resolves rapidly, Wistuba et al. have shown that genetic alteration of airway lining cells observed in current smokers is not reversed in former smokers (JNCI 1997; 89:1336-73). Progression to lung cancer is probably only slowed, but not reversed by removal of the promotional stimuli of smoking. Major medical centers (Beth Israel, MD Anderson, Cancer 1996; 78:1004-10) now report similar numbers of new lung cancer cases from former as from current smokers. Former smokers, having followed the cessation advice of the medical establishment, remain at risk of lung cancer and are likely to benefit greatly from validated lung cancer screening (Cancer. 2000 Dec 1;89(11 Suppl):2506-9).

II. Body

A. Start-up: Study Activation, 0-3 Months

1. Approval: The protocol, informed consent and data collection forms were completed and this study was approved by Moffitt/USF IRB on November 5, 1998, with conditional approval by Army Regulatory Compliance on December 23, 1998. The protocol was resubmitted with amendments covering novel methods of sputum preservation to the Moffitt/USF IRB and received Army Regulatory Compliance final approval and study activation on June 10, 1999.

2. Space Renovation: Two spirometry/sputum induction facilities were originally established. The facility at the Lifetime Cancer Screening (LCS) Center is fully operational. This facility includes a spirometry screening station, a laminar-flow sputum induction hood, and a biosafety cabinet for sputum specimen processing. Interviews and blood drawing also take place in this space. During 2001, a helical CT scanner was installed so that the entire Cohort screening process now can take place at LCS. The screening station at the James A Haley VA Hospital was used primarily for spirometry screening of volunteers identified through the VA Respiratory Division. A large number (n=1259) of Respiratory Division patients were screened and we have now exhausted that patient population for potential study participants. During 2000, the screening station at the James A Haley VA Hospital was closed.

3. Equipment Purchased: At start-up, several major pieces of equipment were purchased to support this study. These include a Helical CT scanner, a Perkin-Elmer 310 gene scanner, and an Arcturus PixCell II Laser Capture Microdissector. Several minor pieces of equipment have also been

purchased, including an induction safety cabinet, nebulizer, and a sputum preparation biosafety hood. In the past two (2) years, no new equipment has been purchased for this study.

B. Recruitment Phase, 3-24 Months

1. Staff Hired: At present, only 1.34 FTE's are funded by DoD to partly support the administrative secretary and the study nurse for participant scheduling and clinical follow-up. The study coordinator and clinical research associate are funded by BeDLAM to oversee the annual follow-up (incidence) screening, data management, and specimen collection.

2. Accrual: The study has met its accrual goal of 1150 eligible subjects $\geq$ 45 years of age with $\geq$ 30 pack years of smoking who have been screened by spirometry (Tables 1 & 2). Our prior sputum/CXR screening trials have shown that in males of this age range with this smoking history, clinical lung cancer will have a 0.7% (7/1000) prevalence and 0.5% (5/1000) annual incidence. In the presence of mild obstruction, the annual lung cancer incidence increases to 1.1% (11/1000) and continues to rise with increasing obstruction. After four (4) screening examinations and estimating a 23% prevalence of obstruction in the study population, we would have predicted 44-50 cases of lung cancer (11-13 cases per year).

At the conclusion of accrual, 3,496 individuals had been screened, 1151 of whom have been enrolled and undergone sputum induction and helical CT screening. Thirty-eight percent of the screened population has been referred for evaluation from the Respiratory Clinic at the James A. Haley VA hospital. This pool of recruits has more ventilatory obstruction than the general population. Exceeding the 23% rate of mild obstruction expected from a (non-clinic) population of cigarette smokers, we find that 59% of our screened population meet the obstruction criterion. By designing the study to include younger, obstructed participants, we have indeed accrued a population at high risk for lung cancer. The observed lung cancer prevalence of 2.3% is more than double that expected among the 1151 first examinations, and the incidence of 0.45% is approximately the same as expected among the 889 follow-up examinations. If this trend continues, 57 cases would be expected to develop in this population by the end of the study, 14% greater than the required sample size.

3. Prevalence Results, Demography: The study population currently consists of 1151 participants who are on-study and were included in the tabulation below. From this population 682 (59%) were obstructed. Twenty-seven (27) of 1151 participants have developed lung cancer (prevalence 2.3%). Twenty-three (85%) of 27 prevalent cases were obstructed. Those who developed cancer were white, 44% were male, with an average 59.7 pack years of smoking and an FEV_1 /FVC of 62%. The age, race, and gender distributions of the cancer cases do not differ from that of the obstructed or total screened populations (Table 3). As might be expected, the medical histories of the obstructed population (and cancer cases) more frequently report the presence of chronic lung diseases. Preliminary comparison of occupational/environ-mental exposures shows no important differences (Data not shown).

4. Incidence Results, Demography: To date, a total of 889 follow-up screening visits have been completed (Table 4). During the follow-up visits, nine cancer cases have been detected either during the first or second follow-up visit. All nine cancer cases were obstructed (mean FEV_1/FVC of 51.2%) and male, with a mean pack smoking history of 86.5 pack years. Eighty-eight percent of the incident cancer cases were white.

5. Preliminary Results, Radiographic Screening: Four hundred and six (35.2%) of 1151 initial and 174 (26.9%) of 646 follow-up helical CT scans have shown an abnormality (non-calcified nodule). Thirteen (48%) of 27 prevalence and 6 (67%) of 9 incidence lung cancers were in stage I (Table 3). This stage distribution is more advanced than reported in the literature. Self-selection by symptomatic individuals is a recognized source of confounding of prevalence results. Only 8 of the 27 (29.6%) of the prevalence cases and 7 out of 9 (78%) incidence cases reported symptoms

6. Preliminary Results, Molecular Airways Markers: Four markers are to be assayed in the sputum of Cohort participants:

A. Sputum Cytology: To date 263 individual subjects have had sputum specimens processed, stained and read by a pathologist (Table 5). Two (12.5%) of 16 cancer cases in the study showed sputum cytology indicative of cancer. For preliminary results see table (below).

B. hnRNP A2/B1 Overexpression: As outlined in the study protocol, ThinPrep monolayer slides are produced from methanol-preserved (PreservCyt) slurries of induced sputum.

At present, we are resolving several issues related to 703D4 immunoassay performance prior to immunostaining the Cohort specimens. We have been funded (Cancer Research Foundation of America) to identify the lung cancer epitope identified by NCI monoclonal antibody 703D4. Specificity of old and new lots of the 703D4 monoclonal are being compared by Western blot to 2 American and 2 Japanese antibodies against hnRNP. Epitope mapping of 703D4 has shown 3 hnRNP binding sites. Peptide oligomers made with these binding site sequences have been used as blocking peptides in immunostaining assays. Seven additional peptides that overlap the epitope have been made. An Elisa assay with 703D4 has identified the epitope within a single 12 amino acid peptide. Following further refinement of the epitope, a new monoclonal will be generated and tested for clinical relevance.

Following the generation of the new monoclonal, slides will be stained (per protocol as follows: Following automated immunostaining (DAKO immunostainer) with the hnRNP A2/B1monoclonal antibody and alkaline phosphatase labeling (LSAB-II, DAKO), individual cells of interest (proplastic, metaplastic and atypical morphologies) are identified by a licensed cytotechnologist. Images of selected cells are acquired at 100 X (Nikon E800 equipped with Princeton Instruments cooled CCD) and quantified automatically for morphologic and densitometric parameters by a workstation running MetaMorph software (Universal Imaging Corp).

C. Loss of heterozygosity (LOH): Eighty-one alleles reported in the literature to be frequently lost in NSCLC or associated with the genes for transforming growth factor ß type II receptor (TBR II) or the downstream signaling SMADs 2 or 4 were examined to confirm their utility in a panel of microsatellite alteration (MA) markers for Cohort specimens. After establishing the PCR conditions (using ^{32}P end-labeling) for the primers at each allele, the primers were applied to archived (non-microdissected) DNA from 43 frozen paired tumor and normal samples. We evaluated microsatellite instability (i.e., shifts; MI) or loss of heterogygosity (LOH), reducing our final panel to 15 markers according to the frequency of these MA on

both tumor tissue and sputum cell DNA templates. After blinded testing of 56 pre-neoplastic screening sputum specimens, lung cancer cases demonstrated LOH at two or more alleles significantly more often than controls. Nevertheless, using microsatellite markers to detect pre-clinical lung cancer in sputum is a challenge due to the large number of positives among cigarette smokers who have not developed lung cancer. While inactivating mutations in genes involved as "caretakers" of different DNA mismatch repair pathways are commonly observed in tumors, each individual may have a different set of defects in these check point genes limiting the screening application of the MA assay.

D. Promoter CpG Island Hypermethylation: Silencing of tumor suppressor genes (TSG) is one mechanism believed to underlie carcinogenesis. TSG silencing may be accomplished through gene alteration (allelic loss or gene mutation). An epigenetic mechanism, promoter CpG island hypermethylation has also been shown to silence TSG transcription (Proc Natl Acad Sci USA, 1996; 93:9821-6). Panels of primers for hypermethylation have been recently published and are under study in our laboratory. We have established the conditions for assay of p16, O^6-MGMT, RAR-ß, and DAP-kinase promoter methylation in our laboratory. Four of seventeen (24%) frozen, paired (non-microdissected) DNA specimens demonstrate p16 promoter hypermethylation in our hands. To assure the quality of archived Cohort DNA, 5 Aliquots of DTT/EDTA/DMSO preserved Cohort sputum (1 cancer, 4 noncancers) have been sent to Dr. Adi Gazdar (Texas Southwestern) for assay of methylation of promoter of RASSF1, RAR- ß, p16, APC, E/H Cadherin. Preliminary results indicate the presence of satisfactorily preserved DNA at the promoter methylation sites in all specimens.

7. *Preliminary Results, Archive:* Two thousand and twenty-two (2022) induced sputum specimens (includes annual repeats) have been prepared with dithiothreitol (DTT) and EDTA, washed in Hanks solution, spun, resuspended and divided into aliquots for freezing with 10%DMSO/90% FBS in liquid nitrogen. CYTYC Thin-prep slide preparations (for pap staining, immunostaining and storage), are to be made from CYTYC PreservCyt (methanol) slurries stored at 4°C. One thousand, nine hundred and ninety-three (1993) spontaneous specimens are also available as preserved slurries. One thousand, one hundred and forty-nine (1149) blood specimens have been processed; the buffy coats have been separated and stored in liquid nitrogen. Six hundred and forty-five (645) buffy coats and six hundred and sixty-three (663) induced sputum aliquots have been processed for DNA. Each specimen (except those in liquid nitrogen or –80 freezer) is bar coded, and computer linked to the database of registration, demographic, medical, smoking, occupational and nutritional history data on each participant.

8. *Database and Lab Specimen Tracking System:* Moffitt Cancer Control Research Computing has developed an Oracle database with a Web front-end to allow registration from multiple sites. This database houses the registration, demographic, medical, smoking, occupational and nutritional history data on each participant. Since data entry is still forms-based, the data system was designed to provide easy, intelligent 'double' entry of data. The system has been programmed to provide data constraints, range and referential checks, and edit capability to keep the data clean. The data system provides tools for subject management (generate barcode labels, track unresolved data, report late forms/specimens, etc.). Finally, the relational database will easily provide data for specific queries and statistical analysis. This Research Specimen Tracking (RST) system has now been requested for

application to the NCI-SPORE-Lung Cancer Biomarker and Chemoprevention Consortium (LCBCC) study.

Moffitt Cancer Control Research Computing also has developed a Laboratory Specimen Tracking System. This study generates a large number of specimens that must undergo multiple assays in several laboratories. The Laboratory Specimen Tracking System (LST) reads the 2-D specimen barcode to log the specimen into the laboratory. The LST has been programmed to assign each type of specimen a 'profile' that specifies what will happen to the specimen in the lab. A 'profile' consists of a number of steps such as: CheckIn/CheckOut, Assay specimen acceptability, Results Reporting and Archive. The LST is able to track the progress of the specimen and let the lab manager know what step the specimen is on, the specimen turnaround time in the lab, and the archive location of the specimen and its offspring including: Slides, Sputum Slurry Bottles, and Cryovials.

III. Key Research Accomplishments

- Developed an infrastructure to identify, accrue, screen and follow a non-diseased community-dwelling population at high risk for lung cancer.
- Developed procedures for collection and preservation of sputum specimens for new (DNA, RNA, protein and morphologic) markers of pre-neoplasia.
- Developed an archive of airways cytologic specimens suitable for evaluation of new (DNA, RNA, protein and morphologic) markers of pre-neoplasia.
- Developed an archive of white blood cells suitable to provide individual control specimens for DNA and RNA
- Developed a potency assay for MoAb 703D4 immunodetection of hnRNP A2/B1 protein expression.
- Identified a panel of 15 LOH markers for sputum lung cancer screening which identifies 84% of lung tumors.
- Completed the initial lung cancer screening of 1151 middle-aged current and former smokers. Approximately 50% are found in stage I, a 3-fold greater frequency of stage I detection compared to the current clinical standard of no screening as reported by the Florida Cancer Registry.

IV. Reportable Outcomes

A. Publications Related to this Study

1. Baker SG and Tockman MS. *Evaluating Serial Observations of Precancerous Lesions For Further Study as a Trigger For Early Intervention.* Statistics in Medicine. In Press.

2. Toyooka S, Fukuyama Y, Wistuba II, Tockman MS, Minna JD, Gazdar AF. *Differential Expression of FEZ1/LZTS1 Gene in Lung Cancers and Their Cell Cultures.* Clinical Cancer Research. 2002 July; Vol 8 2292-2297.

3. Chirikos T, Hazelton T, Tockman MS, and Clark R. *Screening for Lung Cancer with CT: A Preliminary Cost-Effective Analysis.* CHEST 2002; May 121:1507-14.

4. Zhou J, Nong L, Wloch M, Cantor A, Mulshine JL, Tockman MS. *Expression of early lung cancer detection marker: hnRNP A2/B1 and its relation to microsatellite alteration in non-small cell lung cancer.* Lung Cancer. 2001; Dec 32(3):341-50.

5. Mulshine JL, De Luca LM, Dedrick RL, Tockman MS, Webster R, Placke ME. *Considerations in developing successful, population-based molecular screening lung cancer.* Cancer. Dec 1, 2000; 89(11 Suppl):2465-7. Review.

6. Tockman MS, Mulshine JL. *The early detection of occult lung cancer.* Chest Surg Clin N Am. Nov 2000; 10(4):737-49.

7. Tockman MS. *Advances in Sputum Analysis for Screening and Early Detection of Lung Cancer.* Cancer Control, Journal of the Moffitt Cancer Center. January/February 2000, Vol. 7, No. 1:19-24.

8. Kennedy TC, Proudfoot SP, Piantadosi S, Wu L, Saccomanno G, Petty TL, Tockman MS. *Efficacy of Two Sputum Collection Techniques in Patients with Air Flow Obstruction.* ACTA Cytologica. July-August 1999; Vol. 43, No. 4:630-636.

B. Abstracts Related to this Study

1. Zhukov TA, Johanson R, Tockman MS. *Discovery of distinct protein profiling specific for lung tumors and pre-malignant lung lesions by SELDI mass spectrometry.* Proceedings of the AACR, Volume 43, March 2002. Page 36, #184.

2. Zhukov TA, Erozan YS, Tockman MS. *Sentinel Cell for Lung Cancer.* 14th International Congress of Cytology, RAI Congress Centre, Amsterdam, The Netherlands. May 2001.
3. Mulshine JL, Tockman MS, Martinez A, Man Y-G, Montuennga L, Hong SH. *Application of Molecular Biology for Early Detection of Lung Cancer.* 1999.

4. Zhou J, Nong L, Wloch M, Zhukov TA, and Tockman MS. *Expression of Early Lung Cancer Detection Marker: hnRNP a2/b1 and its Relation to Microsatellite Instability in Non-Small Cell Lung Cancer.* Proc. AACR, April 1999, 40:140-141

5. Truncale T, Zhou J, Zhukov TA, Muñoz-Antonia T, Antonia S, Muro-Cacho C, Tockman MS. *Evaluation of TGF-ß II Receptor Expression (TßR-II) and a Common Signaling Mediator SMAD4 in NSCLC.* Proc. AACR, April 1999, 40:337.

6. Falestiny MN, Cardona JJ, Zhou J, Zhukov TA, Nong L, Solomon DA, Tockman MS. *Transforming Growth Factor ß Type II Receptor Expression in Non-Small Cell Lung Cancer, Viral Transformed Bronchial Cells and Normal Bronchial Epithelial Cells: A Comparative Study.* Chest (Suppl); November 1998.

7. Tockman MS, Saccomanno G, Michels R, Zhukov TA, Erozan Y, and Gupta P. *Sentinel Cell for Lung Cancer.* 6th SPORE Investigator's Workshop; July 1998.

C. Presentations Related to this Study

December 8-10, 1998	***International Conference on Prevention and Early Diagnosis of Lung Cancer,*** Johns Hopkins Lung Project and Immunocytochemical Screening for Lung Cancer. University of Varese and University of Massachusetts Medical School, Varese, Italy.
February 12, 1999	***ALCASE Workshop – Lung Cancer: A Revolution in Care,*** Technology in Early Diagnosis of Lung Cancer; Embassy Suites, Tampa, Florida
April 26, 1999	***1999 ALA/ATS International Conference Program,*** Early Sputum Marker for Lung Cancer (hnRNP); San Diego Convention Center, San Diego, California
April 30, 1999	***Pharmacology Seminar Program,*** Detection and Immunostaining of the Lung Cancer Sentinel Cell.: University of Pittsburgh, Pennsylvania.
September 13, 1999	***Advanced Cancer Detection Center,*** External Advisory Committee; Moffitt Cancer Center, Tampa, Florida
September 30th to October 3, 1999	***The First International Conference On Screening for Lung, Cancer,*** Cornell University, New York
October 9-13, 1999	***Annual Congress of the European Respiratory Society,*** Dysregulation of the Cell Cycle in Lung Cancer; Madrid, Spain
October 15-16, 1999	***Molecular Biomarkers Workshop***, Roy Castle Lung Cancer Foundation, Liverpool, England
October 26, 1999	***Screening of Lung Cancer Conference***, Gaithersburg, MD
October 31, 1999	**7th Annual Scientific Assembly of the American Association of Bronchology,** New horizons in cytological based early detection in lung cancer, Chicago, IL
February 9, 2000	***International Symposium on Early Detection of Lung* Cancer,** Molecular Screening Program: Past, Present, and Future, Tel Aviv, Israel
February 27-29, 2000	***International Agency for Research on Cancer, Use of Biomarkers in Chemoprevention of Cancer,*** Lung Cancer: Intermediate Effect Markers, Heidelberg, Germany

March 20, 2000	***Cahan Lectureship at Memorial-Sloan Kettering,*** Molecular Screening for Lung Cancer, New York, NY
April 12, 2000	***Early Detection Research Network Site Visit at H. Lee Moffitt Cancer Center & Research Institute,*** Organization of BeDLAM, Tampa, FL
June 16, 2000	***Wayne State University Cancer Conference,*** Sputum in 2000: Hypothetical Advantages, Practical Limitations, and Novel Approaches, Detroit, MI
June 22, 2000	***Reducing Lung Cancer Mortality: Actions for the New Millenium,*** Sputum Based Detection of Preinvasive Lung Cancer, Washington, DC
June 27, 2000	***Roy Castle Lung Cancer Foundation and H. Lee Moffitt Cancer Center, Quest for the Cure,*** Lung Cancer Screening and Early Detection: Spiral CT Scanning and Molecular Markers, Tampa, FL
July 19, 2000	***H. Lee Moffitt Cancer Center/USF Lung Cancer Conference,*** Epidemiology and Early Detection of Lung Cancer, Coeur d'Alene, ID
July 19, 2000	***H. Lee Moffitt Cancer Center/USF Lung Cancer Conference, The*** Management of Pre-Clinical Lung Cancer, Coeur d'Alene, ID
September 12, 2000	***IASLC 9th World Conference on Lung Cancer,*** Cellular Targeting in the Molecular Diagnosis of Lung Cancer, Tokyo, Japan
October 24, 2000	***66th International Scientific Assembly of the ACCP,*** San Francisco, CA
	ACCP Post Graduate Course, Screening and Early Detection of Lung Cancer
	Meet the Professor, Sputum Detection of Early Lung Cancer: Hypothetical Advantages, Practical Limitations, and Novel Approaches
October 27, 2000	***Cornell CT Conference***, Sputum Detection of Early Lung Cancer: A Compliment to Helical CT , New York, NY
March 7-8, 2001	***Lung Cancer Early Detection Workshop***, National Cancer Institute/ American Cancer Society, "New Frontiers of Screening Science". Rockville, MD
March 24-25, 2001	***Second Annual – A Practical Pulmonary Review for Primary Care Providers***, University of South Florida/Department of Veterans Affairs, James Haley, "Early Recognition of Lung Cancer". St. Pete Beach, FL

June 20-22, 2001	***Early Detection Research Network***, National Institute of Health/National Cancer Institute, "Lung Cancer Screening Update" and "Industrial Partnership with EDRN", Washington, DC
June 26-July 2, 2001	***Second International Lung Cancer Molecular Biomarkers Workshop*** "A European Strategy for Developing Lung Cancer Molecular and Clinical Diagnostics in High Risk Populations, Roy Castle Lung Cancer Foundation, "Sputum in 2001: Hypothetical Advantage Practical Limitations, and Novel Approaches" and "Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers" Liverpool, England
August 7-12, 2001	***3rd International Conference on Prevention & Early Detection of Lung Cancer,*** International Association for the Study of Lung Cancer, "Cellular Approaches to Lung Cancer Detection" and "Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers". Rejkjayik, Iceland
October 13-17, 2001	**EDRN Scientific Workshop,** Seattle, WA
October 26-29, 2001	**5th International Conference on Screening for Lung Cancer**, New York, NY
December 5-6, 2001	**NCI Grant Review Meeting RFA CA-02008 Chemoprevention of Tobacco-related Cancers in Former Smokers: Preclinical Studies,** Washington, DC
February 3-5, 2002	**EDRN Steering Committee**, Houston, TX
March 10-15, 2002	**New Frontiers in Cancer Detection & Diagnosis (EDRN/ Gordon Research Conference)**, Ventura, CA
April 5-7, 2002	**6th International Conference on Screening for Lung Cancer**, Paris, France
June 13, 2002	**NIH Women Tobacco & Cancer Steering Committee**, Besthesda, MD
June 22, 2002	**Great Cancer Roundup: Lung Cancer Screening & Prevention Conference**, Los Angeles, CA
September 3-5, 2002	**6th EDRN Steering Committee,** Ann Arbor, MI
October 11-15, 2002	**Molecular Targets in Cancer Therapy**, St. Petersburg, FL
October 18-20, 2002	**7th International Conference on Screening for lung Cancer**, New York, NY

October 28-30, 2002 **1st International Lung Cancer Conference**, Beijing, China

VI. Funding Received Based Upon Work Supported by this Award

1. "The Biomarker Development Laboratory at Moffitt" (NCI-CA 84973, M. Tockman, PI, 1st year/Total award $413,720/$1,903,827).
2. "Identification of the lung cancer epitope identified by the monoclonal antibody 703D4" (Cancer Research Foundation of America, M. Gruidl, PI, Total award $38,950)
3. J. Park, PI, NCI-EDRN, Total award $98,000.

VII. Conclusion

The Markers of Transformation in Airways Epithelial Cells from a Cohort of Obstructed Smokers and Former Smokers (DoD Cohort Study) has completed its desgined accrual and is preparing to report the prevalence lung cancer screening experience. This research question addresses the most common cause of cancer death and the only common cancer for which no screening is available. Second, the archive of radiographs, sputum and blood cell specimens provides an infrastructure for other investigators at Moffitt and across the nation. The recent award to Dr. Jong Park of an NCI Early Detection Research Network grant was based on the availability of the Cohort archive. Similarly, the collaboration with SPORE investigators at Texas Southwestern (Drs. Gazdar and Minna) and at Johns Hopkins (Drs. Baylin and Herman) are based upon the availability of Cohort specimens. The prospective design, innovative methods and careful execution of this study make it a valuable scientific contribution.

Table 1

Total Population Demographics

Subjects Enrolled (*N*=1151)	Obstructed (*n*=682)	Unobstructed (*n*=469)	P-Value
Age (y) +/- SD	62.0 +/- 8.3	57.6 +/- 8.0	P<0.0001
Sex (M/F)	414/268	270/199	
Average Pack Years (years) +/- SD	62.1 +/- 27.3	51.6 +/- 22.5	P<0.0001
Race No. (%):			
African American	24 (3.52)	13 (2.78)	
American Indian, Eskimo	3 (0.44)	*	
Asian or Pacific Islander	1 (0.15)	*	
Eastern Indian American	1 (0.15)	*	
White Hispanic	11 (1.62)	9 (1.9)	
White Non-Hispanic	639 (93.7)	446 (95.1)	
Other	3 (0.44)	1 (0.2)	
Average FEV1/FVC (%) +/- SD	57.5 +/- 10.7	77.3 +/- 4.4	P<0.0001

Table 2

Moffitt Cohort Study Results

	Study Design	**Actual (as of 10/31/02)**
Screened with Spirometry:	5000	3496
Eligible ~ screened with CT and Sputum:	1150 (23%)	1151 (33%)
Expected Positive Prevalence Screens:	230-460 (20-40%)	406 (35%)
Expected Cancers:	12-13 (1.1%)prevalence 12-13 annual incidence x 4	27 (2.3%) Prevalence 9 (1.0%) Incidence
Exp. Stage Distribution:	80% Stage 1	**Prevalent Cases:** Stage I: 13 (48.1%) Stage II: 2 (7.4%) Stage III: 3 (11.1%) Stage IV: 5 (18.5%) Limited SCLC: 2 (7.4%) Extensive SCLC: 1 (3.7%) Lymphoma: 1 (3.7%) **Incident Cases:** Stage I: 6 (67%) Stage II: 1 (11%) Stage IV: 1 (11%) Extensive SCLC: 1 (11%)

Table 3

Demographic Characteristics of Prevalent Lung Cancer Cases

Prevalent Lung Cancer Cases (*N*=27)	Obstructed (*n*=23)	Unobstructed (*n*=4)
Age (y) +/- SD	64.7 +/- 7.8	64.0 +/-10.2
Sex (M/F)	11/12	1/3
Average Pack Years (years) +/- SD	62.0 +/- 24.5	47.1 +/- 4.1
Race No. (%):		
African American	*	*
American Indian, Eskimo	*	*
Asian or Pacific Islander	*	*
Eastern Indian American	*	*
White Hispanic	1 (4.3)	*
White Non-Hispanic	22 (95.7)	4 (100)
Other	*	*
Average FEV1/FVC (%) +/- SD	60.4 +/- 10.6	72.3 +/- 0.2
Percent of Cancers in Population Screened:	3.4%	0.85%
Percent of Total Prevalent Cancers:	85.2%	14.8%
No. (% of cancers) [% of Screened] of Lung Cancer Cases in Stage:		
Stage I (NSCLC)	11 (47.8) [1.6]	2 (50) [0.43]
Stage II (NSCLC)	2 (8.7) [0.3]	*
Stage III (NSCLC)	3 (13.1) [0.44]	*
Stage IV (NSCLC)	5 (21.7) [0.73]	*
Limited Small Cell	1 (4.4) [0.15]	1 (25) [0.21]
Extensive Small Cell	*	1 (25) [0.21]
Lymphoma	1 (4.3) [0.15]	*

Table 4

Demographic Characteristics of Incident Lung Cancer Cases

Incident Lung Cancer Cases (*N*=9)	Obstructed (*n*=9)	Unobstructed (*n*=0)
Age (y) +/- SD	69.1 +/- 6.6	*
Sex (M/F)	9/0	*
Average Pack Years (years) +/- SD	86.5 +/- 23.6	*
Race No. (%):		
African American	*	*
American Indian, Eskimo	1 (11)	*
Asian or Pacific Islander	*	*
Eastern Indian American	*	*
White Hispanic	*	*
White Non-Hispanic	8 (89)	*
Other	*	*
Average FEV1/FVC (%) +/- SD	51.2 +/- 12	*
Percent of Cancers in Population Screened:		
No. (% of incident cancers) of Lung Cancer Cases in Stage:		
Stage I (NSCLC)	6 (67)	*
Stage II (NSCLC)	1 (11)	*
Stage III (NSCLC)	*	*
Stage IV (NSCLC)	1 (11)	*
Extensive Small Cell	1 (11)	*

Table 5

Cohort Sputum Cytology Results

Encounter	Number	Normal	Reg. Met	Mild Dysplasia	Mod. Dysplasia	Squamous Cancer	Adeno Cancer	Unsat.
1	184	38 (21%)	117 (64%)	14 (8%)	3 (2%)	1 (0.5%)	1 (0.5%)	10 (6%)
2	56	6 (11%)	41 (73%)	3 (5%)	N/A	N/A	N/A	6 (11%)
3	7	1 (14%)	6 (86%)	N/A	N/A	N/A	N/A	N/A
Cancer Cases	16	10 (62.5%)	1 (6.25%)	1 (6.25%)	1 (6.25%)	1 (6.25%)	1 (6.25%)	1 (6.25%)

Moffitt Cancer Network
Principal Investigator: Jeffrey P. Krischer

INTRODUCTION:
The Moffitt Cancer Network's (MCN) goal is to provide up-to-date oncology related information, resources, and education to oncology health care providers and researchers for the prevention and cure of cancer. Consistent with the aims of the Advanced Cancer Detection Center, the MCN provides access to educational programming, cancer control and clinical protocols, and a mechanism to exchange patient focused information leading to the improved detection and treatment of cancer. The MCN is health care provider focused and complements an array of existing public/lay information sources available elsewhere. It is built around the concept that oncology expertise is geographically centralized, multidisciplinary in nature and of limited availability. The MCN addresses these constraints by increasing availability through a World Wide Web-based design that enables wide access from many geographic locales. The objectives of this project are to:

Collect and organize cancer information to provide educational content to physicians and other health care providers,
Develop and implement software to encode video and audio to enable viewing over the Internet at a range of speeds (bandwidths),
Implement a mechanism to deliver continuing education credits through on-line testing and automated submission/evaluation,
Design and create a web page to permit easy sorting, searching and selection of educational programming,
Design and create a web page to deliver physician referral information that includes submission of an electronic case record consisting of text and imaging data, and
Provide access to case conferencing from remote locations using easily available audio/video to the desktop.

BODY:

Task 1. Collect and organize cancer information to provide educational content to physicians and other health care providers. (Months 1-60).

A schedule of events is determined in coordination with the Moffitt Office of Conference Planning, the Moffitt Multimedia Educational Resources Center, the USF Department of Education, the USF department of Continuing Medical Education and independent researchers wishing to present. These events include: Grand Rounds, the monthly meeting of the Cancer Control Research Interest Group (CCRIG), Tech Topic (for medical information technology staff), a number of national and local oncology conferences, as well as a number of JCAHO requirements for in-service education for nurses, physicians, and other hospital staff.

The MCN currently has 496 presentations in its library, increasing at a rate of 16 presentations per month on average (an increase from 6.8 per month the previous year). Additionally, 13 conferences sponsored by USF and Moffitt are also currently available online.

Schedule videographer coverage of grand rounds and research conferences.
The Network Coordinator in cooperation with Moffitt Department of Education and the Moffitt Multimedia Educational Research Center compiles a schedule of events. This schedule is used to determine the scheduling needs of the MCN videographer. The MCN videographer provides audio and video capture of these events digitally and to 90-minute DVCAM (Digital Video Camera) tapes when appropriate. Whenever possible MCN captures presentations electronically without the use of videotape.

Coordinate notification of nursing, pharmacy and other health care providers continuing education presentations.
The Moffitt Department of Education notifies the MCN of all continuing education presentations and obtains a release from all speakers that permits the distribution of their respective presentation by the MCN.

Organize the videotaping of faculty scientific presentations for national oncology conferences.
The notification and videotaping of national oncology conferences is scheduled in accordance with the system mentioned above, developed in coordination with the MCN and the Moffitt education department. A number of conferences have been added to the MCN library. These presentations are digitized and are made available on the MCN website. The presentations acquired by this activity are codified by a medical librarian, searchable by subject and grouped by their respective conference title.

Coordinate with the Department of Education notification and scheduling of relevant conferences.
The Moffitt Department of Education notifies the MCN of all relevant conferences and the MCN videographer is scheduled in accordance with the videotaping needs of each conference.

Task 2. Develop and implement software to encode video and audio to enable viewing over the Internet in a range of speeds (bandwidths). (Months 1-60)

Explore the application of the Tag development software to support multiple video connections and the impact on network bandwidth.
The MCN has developed a process of digitizing presentations using the Digital Renaissance Tag Composer. Through this process MCN is able to stream presenter's slides and audio simultaneously by using a Synchronized Multimedia Integration Language (SMIL) script file. MCN originally encoded presentation for distribution over ISDN speeds of 128k and modem speeds of 56k. The encoding process used previously created two-network streaming formats, one for ISDN speed connections at 128 kilobytes per second and a second format for current modem technology speeds of 56 kilobytes per second or less. Using the Real media server software, users linking to a presentation acquire the format (streaming speed) appropriate for their connection bandwidth. The server and the user's player handle this process automatically.

Late in August 2000 MCN determined that the ISDN format was redundant, as it did not offer any significant improvement over the modem format due to the low frame rate of the

presentations being developed (sometimes as low as one frame for every three minutes), and MCN has discontinued the encoding an ISDN bit rate media file and thus lowering the production time.

In July of 2000 MCN began to explore the use of the Microsoft Media suite of tools for development of online course content. Microsoft Media provides significant advantages in bandwidth reduction, production and administration time, and potential audience. The MCN has since migrated all processes to Microsoft Media. Windows Media supports a process called Multiple Bit Rate (MBR) video. Put simply, MBR video allows MCN to create a presentation geared toward either low (those users below 128k) or high (those users above 128k) bandwidth. The software determines the minimum speed required by the presentation to stream then negotiates between the client computer (the user) and the server the most bandwidth conserving connection. Using MBR video we are able to stream presentations at 28-32k which previously required 56k+ using Real media. In March of 2000 MCN began the process of converting all assets previously developed in Real media to the Microsoft Media format to better serve our users.

In August of 2001 MCN completed the conversion off all assets to Microsoft Media and began using Windows Media version 7, this provided significant quality improvements over Windows Media version 6.4 while reducing bandwidth requirements.

In the past year the MCN has begun using Microsoft Media 8, which provides higher quality at a lower bandwidth than Window Media 7. With each reduction in bandwidth requirements our potential audience increases considerably.

Evaluate alternative connectivity models, including cable modem connections or access to cable networks as a means to enhance distribution of educational content.

The MCN has evaluated multiple alternative connectivity models, including cable modems, ISDN, ADSL, and traditional T1 & T3 service lines. We have found that cable modems are an excellent method of distributing educational content. Cable modems and ADSL provide a low cost, high bandwidth alternative for the user. This allows educational content to become more dynamic and interactive increasing the quality and effectiveness of the educational activity.

Evaluate the Internet 2 as to its availability to sustain the necessary bandwidth for the Moffitt Cancer Network.
The MCN has evaluated Internet 2 and found it is ideal mechanism for transporting images, streaming video to and conducting case conferences with other researchers and physicians.

Resolve firewall and security issues to provide secure communication for clinical data as well as to adequately deal with subscriber/user requirements for security to permit desktop access.
A firewall has been put in place to ensure secure communications for clinical data and to address user security issues. Moffitt IT, in coordination with the MCN has developed a firewall policy relating to streaming media.

The Moffitt Cancer Center uses key fob technology in conjunction with a secure ID for access to information through the firewall.

Currently, data will only be available at pre-selected times and with pre-selected permission or authorization levels.

Uniform Resource Locator based on specific one-time virtual names.
All prerecorded media is encrypted when necessary and will have a unique access requirement for specific use. Users have no direct access to media assets and are provided a virtual link to the assets by a database driven web front end. Additional security methods are still being researched and firewall security is a priority.

Expand the number of Authorized users to the Moffitt Cancer Network.
Expansion of authorized users is critical to the digital convergence with MCN's ongoing research and development. We are now capable of delivering "On-demand", encrypted, and live media to desktops both user specific and publicly when appropriate. In addition, with the recent addition of continuing credit hours for nursing, we have opened a huge medical audience for MCN. It should be noted that there is no requirement to register or become authorized in order to watch most presentations available on the MCN.

Authorized users increased from 2 to 16 in the year 2000, and increase of 800%.

In mid 2001 a distinction was made between "authorized" and "registered" users. Authorized users are groups of predetermined people who are authorized to view a particular type of content. Registered users are either authorized users who have taken the time to register or non-authorized users who have registered for CME purposes. Authorized, registered users (previously referred to as just "authorized" users) increased from 16 to 68, and increase of 425%, in the year 2001.

Due to recent outreach programs our user base continues to grow. In 2001 the number of authorized, registered users increased from 68-90, an increase of 32%. The number of fully registered users continues to rise at a steady rate. New programs with Moffitt affiliate hospitals established in 2001 generated even greater number of authorized, registered users.

Registered, authorized users increased from 90 to 237 in 2002. This represents an increase of 263%.

The number of authorized or registered users reflects a segment of the utilization of the Moffitt Cancer Network. The overall usage statistics are a more valuable statistic to determine utilization. The statistics (below) show a regular progression in utilization over the past year of the Moffitt Cancer Network. The statistics are separated into internal (users internal to Moffitt Cancer Center) and external (those accessing via the internet). The combined value displays the number of presentations watched and the average number of presentations watched per user. Important to note is the number of sessions (visits) and number of presentations watched per month. The statistics show a regular increase from month to month in site utilization.

MCN Statistics 2001/2002

As of 02/08/02

Web Stats

	Sep 01	Oct 01	Nov 01	Dec 01	Jan 02	Feb 02	Mar 02	Apr 02	May 02	Jun 02	Jul 02	Aug 02	Total
Internal													
Sessions	190	372	699	315	280	430	295	417	590	723	709	1035	6055
Hits	679	2689	5298	1998	1814	3215	1840	4327	6072	6761	5287	8228	48208
H/S Ratio	3.574	16.906	7.579	6.343	6.479	7.477	6.237	10.376	10.292	9.351	7.457	7.950	7.961
Unique Vis	106	176	398	163	134	196	156	201	286	338	415	620	265.75
S/U Ratio	1.792	2.114	1.756	1.933	2.090	2.090	1.891	2.075	2.063	2.139	1.708	1.669	
External													
Sessions	716	800	708	913	1167	1300	1499	1233	1339	1473	1771	2253	15172
Hits	1743	2552	2649	3676	4523	5876	6074	4648	4538	5483	6020	10086	57868
H/S Ratio	2.434	3.190	3.742	4.026	3.876	4.520	4.052	3.770	3.389	3.3.722	3.399	4.477	3.814
Unique Vis	375	426	489	480	593	793	832	781	802	779	887	1129	697.16
S/U Ratio	1.909	1.878	1.448	1.902	1.968	1.639	1.802	1.579	1.670	1.891	1.997	1.996	
Combined													
Pres Watch	89	114	222	186	276	441	354	239	94	337	401	674	3427
P/U	0.19	0.19	0.25	0.29	0.38	0.45	0.36	0.24	0.09	0.30	0.31	0.39	

*H/S Ratio represents the average amount the users explorers the site

*S/U Ratio represents the average number of times users returns

*P/U Ratio represents number of videos the average user watched that month

*Unique visitor total is the mean unique visitors per month for the year

Task 3 Implement a mechanism to deliver continuing education credits through on-line testing and automated submission/evaluation. (Months 1-60).

Arrange for automated notification of Department of Education staff for each new presentation selected for the Moffitt Cancer Network.

Prior to inclusion in the MCN, the Moffitt Department of Education reviews each presentation for quality of educational content.

Establish ongoing procedures to obtain releases, objectives and CME questions to implement to permit encoding of presentations and inclusion onto the Moffitt Cancer Network.

Presenters sign a release to rebroadcast prior to the videotaping of their presentation. The Moffitt Department of education works closely with the presenter and the MCN to establish objectives, determine appropriate CME questions and evaluate the overall quality of the educational content of the respective presentation. Upon the completion of this work, all information is passed to the MCN for inclusion into the MCN website for delivery to the user.

Create documentation and procedures to collect appropriate demographics on individuals desiring CME and implement electronic automated notification of our Continuing Education Office to authorize and verify CMEs earned.

Appropriate demographic information is collected from all individuals wishing to receive CME credit for physicians or nurses contact hours. Upon completion of a CME credit or contact hours, the MCN staff is electronically notified. The results of the activity are graded electronically and

the information is forwarded to the USF Education Department if a CME credit or contact hour was in fact earned.

In early 2001 MCN developed a process whereby all relevant information pertaining to the educational activity and credit received is transmitted via an encrypted data string directly into the USF Continuing Education certificate-processing cue upon satisfactory completion of credit requirements. This eliminates a number of steps while reducing the probability of error. MCN currently uses a redundant system whereby USF Continuing Education records are audited each quarter against MCN records to ensure proper certificate issuance.

Automatically link the Cancer Library to the acquisition process so that they are aware of new acquisitions and receive opportunities to extract key words for indexing, sorting and searching.
Upon the completion of the digitization of a presentation, the digitized presentation is forwarded to the Cancer Center Librarian for review. The Cancer Center Librarian extracts key words used for indexing, sorting and searching presentations on the MCN website. These keywords are added to the MCN website database for each respective presentation.

Extend the CME process to include CEUs for nursing and pharmacy.
The MCN currently offers CME credit for physicians as well as contact hours for nursing continuing professional education (CEU). The certifications are provided in cooperation with the USF College of Medicine and Nursing, respectively. We are continuing to explore the applicability of the content to other healthcare providers, such as pharmacists, and the requirements to offer continuing education credits.

Expand the educational content offerings to include mandatory requirements for risk analysis, HIV, infection control, etc.
The MCN has expanded the educational offerings to include a number of JCAHO requirements for nurses, physicians and staff. These offerings are available internally to all personnel via the Moffitt Cancer Center Intranet. Major mandatory education such as Domestic Violence, HIV/AIDS, and Bioterrorism are available to external users as well.

Task 4. Design and create a web page to permit easy sorting, searching and selection of educational programming. (Months 1-24)

Organize educational content along primary audience lines and develop a key word searching algorithm to subset for presentations.
An algorithm has been developed allowing keyword searching. The keywords are determined during the review of the presentation by the cancer center library. A new algorithm was developed in 2001 allowing a more efficient search. The MCN website provides chronological ascending/descending, keyword search, search within results, and presenter last name, first name searches.

Implement a database for key words according to a standard nomenclature, utilizing NLM MeSH headings, cancer site, etc.

A keyword database has been created and is used by the MCN website for searching. The keywords are determined by the Cancer Center Librarian prior to the addition of a presentation to the MCN. The keywords are based on NLM MeSH standards.

In late 2001 the MCN began to track user searches to gain a better understanding of how users search the website. The information gathered has led us to add not only MESH keywords, but layperson keywords as well.

Expand implementation of Active Server Page (ASP) extensions to the multimedia hypertext (HTML) by adding onto the 'back-end' of the Web application i.) procedural language scripting and ii.) the ability to exchange information with a fully functioning database.
ASP has been used throughout the site to produce dynamic, database driven web pages. ASP is used in all areas of the site to set procedural paths, increase security and generate dynamic content from the MCN databases.

Expand and refine the JET database to incorporate user defined search phrases that are located within a variety of fields associated with the database, including a textual 'objectives' section, MeSH headings, cancer site, canned search categories, etc.
The MCN has increased the capability of the Jet database to allow user defined search phrases. These phrases search for matches in the textual 'objectives' section, MeSh headings (keywords), cancer site, and canned search categories.

Monitor utilization by remote site to evaluate the frequency and demand for various types of educational content to permit refinements and revisions to improve offerings.
The MCN gathers extensive information in regards to use of the MCN website. This information includes website traffic, which asset was accessed, time spent, keywords searched for, the number of presentations watched, for credit or not, and the frequency with which each presentation is watched.

Task 5. Design and create a web page to deliver physician referral information that includes submission electronic case record consisting of text and imaging data. (Months 1-36)

Develop and implement a database to archive text and imaging data for retrieval by consulting Cancer Center physicians and integration with Moffitt Cancer Center clinical information systems.
Moffitt has a DICOM server which, when combined with secure Internet protocols, may be used to transmit and receive DICOM-compliant images to and from partners on the Internet. These images are securely relayed to and from Moffitt's PACS viewing stations. This technology has been proven to work in experiments with the Haley Veterans' Administration Hospital and Cornell University. Radiology is currently working with Morton Plant Hospital to develop a permanent, Internet-based method of exchanging patient radiographic images.

Develop a structured computerized clinical case description that provides a minimally relevant set of data that describes a clinical case for second opinion and consultation.

Efforts to date have focused on image transfers and the capability to be DICOM compliant. Appropriate mechanisms have been developed along with interfaces to hospital PACS and Radiology Departments. Exploration is currently underway to exchange textual information and establish the computerized clinical case record.

Acquire hardware and software to provide audio and video real time and time shifted streaming of case conferencing to remote locations for user viewing over secure communication links.
In July 2000 MCN procured rack mounted dual processor servers and audio/video equipment for the purpose of providing both real-time streaming of media as well as simultaneous capture of that media for archive.

In December 2000 MCN began exploring the use of low-cost, low bandwidth one-way and two-way case-conferencing equipment. This is equipment would allow the patient to contact and conference with their respective physician without leaving their home. A preliminary trial of the equipment and its functionality, conducted in 2001, was successful.

In October 2001 MCN began streaming a monthly genetics case conference to our affiliate hospitals.

MCN is now evaluating the use of a synchronous conferencing system called Lotus Sametime for the monthly genetics case conference. We believe this will improve the efficacy of the conference and by allowing remote users to interact with the geneticist.

Establish the necessary gateways and bridges to provide connections at a range of bandwidths to support remote connectivity.
All processes are controlled remotely and is designed for live to archive times of no more than 5 minutes. In other words, five minutes after a live broadcast event is completed, an "On-Demand" rebroadcast will be available to specific users. The former being broadcast via secure port and virtual link and the latter are encrypted for use with a specific key.

MCN is currently reviewing equipment requirements to increase capacity. Additional equipment is expected to be purchased.

Design and implement web-based front ends to Moffitt Cancer Center clinical systems to permit secure access to patient information of patient's referred or submitted to case conferencing or second opinions.
Moffitt is in the process of a Cerner Clinical record system implementation. Upon the completion of this project, restricted access to case information could be made available via the web.

Task 6. Provide access to case conferencing from remote locations using easily available audio/video to the desktop. (Months 1-48)

Complete telegenetics experiment to assess feasibility and acceptability of this format for the exchange of clinical information.

Telemedicine began to accrue subjects on May 11, 2000. Accrual for the study was met in 2002 (60 individuals).

We are in the process of preparing an article describing the study. Data suggests the use of telemedicine for counseling is acceptable and just as effective as face-to-face care.

Implement additional sites to expand this program and resolve billing issues within the context of existing laws and regulations regarding telehealth and teleconsultation programs.
A preliminary structure has been put in place for support, however legal limitations existing within the state hinder rapid progress on developing a program. New legislation is expected during the next legislative session that will have a direct bearing on regulations governing telemedicine.

The genetics department is currently in discussions with five central Florida hospitals to expand the Moffitt genetics program to their locations via telemedicine.

MCN plans to expand the telegenetics study into the national Community Clinical Oncology Program over the coming year.

Establish the necessary gateways and bridges to provide connections at a range of bandwidths to support remote connectivity.
MCN is implementing two strategies, traditional videoconferencing and Sametime web based videoconferencing at the desktop. Sametime provides a low cost, secure mode of communication, primarily aimed at researchers and M.D.s involved in case conferencing. Traditional videoconferencing provides a widely adopted videoconferencing modality and therefore use of the equipment does not necessarily mean the adoption of new technology for remote centers.

Develop tunneling or other secure links to resolve firewall issues regarding LAN configurations at both the Moffitt Cancer Center and remote sites.
Moffitt is using Virtual Private Networks with key fob and biometric authentication technology. A Cisco Multimedia Conferencing Server is being placed in tandem with the firewall to provide a secure single point of access through the firewall for videoconferencing.

Acquire and install technology in conference centers where case conferencing generally occurs for selected clinics to permit retrieval and display of multiple images and clinical data submitted for this purpose by remote users.
For each site, a detailed plan of operations has been developed to establish the capability to schedule and transmit signals for MCN distribution. MCN has implemented streaming equipment for Clinical and Research presentations given at the center. MCN technology is being applied to a research tower and clinic, now under construction, to be completed in early 2003.

As of March 2001, MCN has successfully completed the installation of case conferencing equipment in two primary conference centers.

Plans for a fully interactive case conferencing center are underway. The center would provide access to digital radiology, relevant patient information, and a host of other technologies.

Assess utilization of this technology to refine and revise formats and improve the quality and ease of remote access.
MCN has made it a priority to improve the quality of its products. Moving towards the use of Microsoft products and its MPEG-4 streaming format has reduced labor and increased quality across the board. MCN has implemented programs for remote control of streaming servers. A migration to XML took place in June of 2002, improving portability of the system. The use of scan converters in capture of educational content has greatly improved quality of the final asset. Finally, changes in its business practices have reduced labor requirements and increased quality and functionality as well as increased the customer base.

MCN continues to work to increase capability and functionality, improving video quality, and lowering bandwidth requirements for the user, while at the same accruing more content and reducing the production time by streamlining and automating the process.

Sametime videoconferencing was implemented to provide low cost case conferencing access to smaller, possibly rural medical centers.

KEY RESEARCH ACCOMPLISHMENTS:

•The Moffitt Cancer Network is available to users and can be found at
http://network.moffitt.usf.edu
•The MCN currently has 496 presentations in its library, increasing at a rate of 16 presentations per month on average. Additionally, 13 conferences sponsored by USF and Moffitt are also currently available online.
•
•All approved Grand Rounds presentations have been taped by the Moffitt Multimedia Education Resources Center (MERC) for over two year preceding this report. The video was previously captured on digital DVCAM 94 minute tapes. Currently we are running in a tape-less environment.
•Since many of the presenters use only 35mm slide for their presentations, a process of creating final production audio/video Real media for streaming via TCP/IP has been developed. This process requires post-production labor and requires the best of the video's individual frames to be captured a second time to recreate higher quality computer images. MCN has made significant progress in this area and as of June 2000 has begun using presenter's PowerPoint files when ever possible to bypass the second image rendering process. This has reduced labor time from 3.5 days to about 5 hours, while increasing image quality noticeably. This labor savings is not realized when presenters are using 35mm film only. This methodology was modified to capture slides, overheads and computer screens digitally without a camera. The new methodology has reduced post-production time to virtually nothing. This allows us to concentrate on acquisition of new material.
•In addition to pre-presentation file acquisition, MCN has begun the development of a presenter packet. When finished, this packet will inform presenters to repeat important questions asked at

the end of events like Grand Rounds and these will be added to the content to be available to medical professionals at the MCN website.

•National oncology conferences have been taped and included in the MCN website database.

•Conferences have been subdivided into their respective presentations and are categorized searchable as well as searchable using the website database Access Jet engine. All conferences are pre-qualified for their ability to become online educational materials by the University of South Florida College of Medicine and, more recently, the University of South Florida College of Nursing.

•MCN began simultaneous live streaming and archiving in late 2001. This process greatly reduces postproduction time while increasing access to live events.

•MCN has completed the move to camera-less and tape-less acquisition of presentations using a host of digital equipment.

REPORTABLE OUTCOMES:

•Patents and licenses applied for and/or issued;

A notice of disclosure has been filed with the USF office of patents in anticipation of the completion of a patent application.

•Presentations

- The Moffitt Cancer Network Vision, Jeffery Krischer, Ph.d. April 2001
- The Moffitt Cancer Network, Lessons Learned and New Directions, Matthew Clark, B.S. October 2001
- The Moffitt Cancer Network 2002, Matthew Clark, B.S. April 2002
- Keyword Indexing: Adding Value to the Moffitt Cancer Network [MCN] Web-based Education, Sue Felber, M.S., May 19, 2002 Medical Library Association Conference, Dallas TX
- No-latency video architecture, efficiency and a new tomorrow for on-line education, Matthew Clark, B.S. June 2002
- Keyword Indexing: Adding Value to the Moffitt Cancer Network [MCN] Web-based Education, Sue Felber, M.S.,June 19, 2002 Tech Topics, Moffitt
- Keyword Indexing: Adding Value to the Moffitt Cancer Network [MCN] Web-based Education, Sue Felber, M.S.,October 19, 2002 Southern Chapter, Medical Library Association
- Disseminating Library Instruction to the Desktop via the Web, Sue Felber, M.S.,October 19, 2002 Southern Chapter, Medical Library Association
- Telemedicine Today and Tomorrow, Matthew Clark, B.S. October 2002

•Abstracts

- J Permuth-Wey, JA Betts, AB Cantor, JP Krischer, R Sutphen: Cancer Genetic Counseling and Testing by Telemedicine - Results of a Feasibility Study (Abstract). American Journal of Human Genetics (2002) 71(4): 343.

CONCLUSIONS:

The purpose of this research is to create processes that allow medical professional to extend their abilities through the use of electronic media. MCN has evolved in pace with the change of that

technology and because of its foresight and its dedication to purpose it has kept ahead of the technology. MCN has realized that streaming media processes are now capable of high definition presentations at low bandwidths and has developed the best possible processes for producing usable educational media delivery using network technology. MCN's research into these processes has revealed the need for specific products and their uses. Several new programs have been developed to address these processes. For example, to cut down on the need for many new employees, MCN has developed a broadcast program that will allow a single user to set start/stop times on a given event at a given location.

Conventional videoconferencing has limitations of cost and support while not meeting security and privacy requirements of HIPAA. Lotus Sametime may be a cost effective means of HIPAA complaint case and video conferencing. Providing second opinion and expert information to referring physicians is an extremely important piece of MCN's research. While continuing education is a given, in the final analysis, it may be in the medical professional interaction that MCN becomes most useful. If it were determined effective Sametime would provide a secure, cost effective case conferencing system that would allow smaller and rural centers as well as individual doctors a means to gain access to Moffitt expertise.

REFERENCES: None

Tampa Bay Ovarian Cancer Study
Principal Investigator: Rebecca Sutphen, M.D.

1. Introduction

The BRCA1 and BRCA2 genes are believed to account for the majority of inherited ovarian cancer, yet few population-based studies have been performed specifically to investigate their role in this deadly disease. The Tampa Bay Ovarian Cancer Study (TBOCS) is a case-case study of incident epithelial ovarian cancer in the geographic region of Hillsborough and Pinellas counties, Florida, comprising an estimated 170 annual cases in women between 18 and 80 years of age. A rapid ascertainment system is utilized. In-person interviews are conducted with all subjects, in order to collect comprehensive data on health behaviors, risk factors, personal and family history; provide genetic counseling; and obtain blood samples. Complete sequencing of the BRCA1 and BRCA2 coding regions is performed to allow assignment of cases (mutation-carriers) and controls (non-carriers); we will thereby determine the prevalence of BRCA1 and BRCA2 germline mutations in this population. The purpose of this initial project is to demonstrate the feasibility of conducting a 5-year successor study of ovarian cancer cases associated with germline BRCA1/BRCA2 mutations, compared with sporadic cases.

The specific aims of this feasibility study and the expanded successor study of incident epithelial ovarian cancer are:

1) to investigate whether and which health behaviors and risk factors differ between germline mutation-associated cases and non-mutation controls;
2) to examine differences in the family cancer history profile of mutation-associated cases and non-mutation controls;
3) to examine differences in tumor characteristics between mutation-associated cases and non-mutation controls;
4) to investigate differences in response to treatment and survival between mutation-associated cases and non-mutation controls;
5) to achieve an 80% participation rate using a unique and comprehensive recruitment design.

2. Body

The study was reviewed by the Surgeon General's Human Subjects Research Review Board (SGHSRRB) on September 27, 2000. Final approval to open the study for enrollment was obtained on December 13, 2000.

Status of tasks included in the approved statement of work are as follows:

Task 1: Preparation for Medical Record Abstractions

Data elements of the medical record abstraction form have been finalized. Design of the medical record abstraction form and the data entry mechanism for pathology data has been completed. This design allows direct data entry of abstracted medical records into the database, followed by independent review of the medical record data by the

pathologist at the time of pathology analysis. This mechanism makes data entry highly efficient while ensuring data quality.

Task 2: Recruitment and Training of Study Personnel

The first recruitment strategy to be implemented involved recruiting all gynecologic oncologists in the region as co-Investigators in the study and training their staff regarding the study. At this time, this first strategy has been accomplished, except that one of the 7 gynecologic oncologists requires additional strategies (described further below) to accomplish recruitment. Additional study personnel are currently being trained. Other recruitment strategies are currently being implemented, including: 1) $100 reimbursement per enrollment is planned to the physician offices to compensate for time, effort and space allocated to this project. This strategy has received USF IRB approval and is being reviewed by the Surgeon General's Research Review Board (submitted June 11, 2001) prior to implementation. 2) recruitment through medical oncologists' offices is being implemented to accrue subjects missed at the gynecologic oncologists' offices, and additional co-Investigators have been added, 3) institutional IRB approval is being obtained at diagnosing hospitals in the study region to allow study staff to obtain names of patients with ovarian cancer so that study staff may assume responsibility to contact ovarian cancer patients through a letter signed by the staff physician, and follow up via phone call to determine interest in participation. By centralizing responsibility for patient contact to study staff, we will decrease responsibilities of local physicians' staff, which will facilitate enrollment and enhance accrual. Approval from the USF IRB for this strategy has been requested. Approval from the Surgeon General's Research Review Board will also be required.

Task 3: Subject recruitment and Data Collection

Based on experience thus far, the study interview appears to be a successful strategy to accomplish explanation of the study, provision of informed consent, enrollment, completion of study questionnaire, genetic counseling, and blood sampling. Medical records have been successfully obtained for all recruits and abstraction performed. Tumor tissue has been successfully obtained from the appropriate surgical locations for all pathology analyses. Blood samples have been successfully obtained for genetic testing and banking for future research.

Task 4: Disclosure of results to the patients

The results of genetic testing and related information (depending on results) have been provided to subjects who elect to receive results. Results of genetic testing have been utilized for assignment of case-control status and matching.

Task 5: Abstraction of Medical Records

Medical record abstractions have been performed for all enrolled subjects. 6 month follow-up data has been obtained for appropriate participants. Data entry and quality control measures are ongoing.

Task 6: Tumor Tissue Analyses

Tumor tissue has been collected for all subjects. Pathology analyses will be performed, data from analyses will be entered into the database, and tissue will then be banked for future research.

Task 7: Follow-up for Survival

6 month follow-up data has been obtained as appropriate. Follow-up contacts will continue for surviving enrolled subjects after 6 months, after 1 year, and annually as funding permits. Data entry and quality control measures are ongoing.

Task 8: Statistical Analyses and report writing

Analyses and reports will be prepared.

3. Key Research Accomplishments

Aim 1: We are successfully collecting data regarding health behaviors and risk factors from all participants via questionnaire instruments and study interview.
Aim 2: We are successfully collecting detailed cancer family history from all participants via questionnaire instruments and study interview.
Aim 3: We have established a successful mechanism to obtain medical records and tumor tissue in order to compare tumor characteristics between mutation-associated cases and non-mutation controls.
Aim 4: We have established a successful follow-up mechanism to obtain data regarding differences in response to treatment and survival between mutation-associated cases and non-mutation controls.
Aim 5: We are implementing additional strategies to achieve 80% participation of eligible cases and anticipate success by summer 2002.

4. Reportable Outcomes

Based on the epidemiologic design of the Tampa Bay Ovarian Cancer Study, funding was awarded by the American Cancer Society for a 3-year companion study to evaluate the role of biologically active lysophospholipids for their potential as biomarkers of ovarian cancer. Preliminary data is promising and shows that certain lysolipids appear to be elevated in the plasma of women with ovarian cancer compared with healthy controls. Based on this preliminary data, we have applied for an R01 to investigate the use of lysolipid measurement for detection of ovarian cancer in a population of women at increased risk of ovarian cancer, including first-degree relatives of women in TBOCS (ovarian cancer patients). Our ongoing contact with women in TBOCS will facilitate the identification and enrollment of their female relatives at increased risk for enrollment in this important study, toward the development of an early detection test for ovarian cancer.

Based on data showing that gene mutations associated with Hereditary Non-Polyposis Colorectal Cancer (HNPCC) are the third leading cause of hereditary ovarian cancer (after

BRCA1 and BRCA2), and the suggestion that ovarian cancer is a "sentinel cancer" in individuals with these gene mutations, funding for the investigation of HNPCC as a companion study of TBOCS has been funded.

5. Conclusion

Epithelial ovarian cancer results in the death of more American women than all other gynecologic cancers combined. The Tampa Bay Ovarian Cancer Study is designed to evaluate the role of the BRCA1 and BRCA2 genes in the etiology, pathology and response to treatment of this deadly disease. Additional recruitment strategies are being implemented to achieve enrollment of 80% of eligible ovarian cancer patients. Current funding supports the initial development of a successful accrual strategy toward a planned 5-year successor study. Based on the design of the feasibility analysis and successor study, a 3-year companion study has been funded to assess the potential of biologically active lysophospholipids as biomarkers in ovarian cancer. The Tampa Bay Ovarian Cancer Study and its companion study represent an important opportunity to evaluate the role of inherited susceptibility to ovarian cancer and evaluate lysophospholipids for their potential as biomarkers of this deadly disease. No similar study has been performed. In order to accomplish these critical goals, continued funding of the current study is required.

Abstract submitted to the annual meeting of the American Society of Human Genetics (October 2002):

Tampa Bay Ovarian Cancer Study – A Population-based Study of BRCA1/2 in Ovarian Cancer.

Tuya Pal, Jeffery P. Krischer, Tricia Holtje, Judith A. Betts, Jenny Permuth Wey, James Fiorica, Edward Grendys, James LaPolla, Hector Arango, Katie Wakeley, Mitchell Hoffman, George Wilbanks, Santo Nicosia, Rebecca Sutphen and the Tampa Bay Ovarian Cancer Coalition

BRCA1 and BRCA2 are believed to account for the majority of hereditary ovarian cancers. Current estimates of mutation likelihood among ovarian cancer patients range from 9.2% (Myriad data) to 11.7% (Ontario population data, the only published population-based data).

To determine the prevalence, spectrum of mutations and genotype/phenotype correlations among ovarian cancer cases, we are conducting a population-based study of unselected incident cases of epithelial ovarian cancer in the geographic regions of Hillsborough and Pinellas counties, Florida (which includes Tampa, St. Petersburg, and Clearwater). Beginning in 2001, we have enrolled 100 women diagnosed with incident ovarian cancer, ascertained through their treating gynecologic oncologists. Medical records and tumor tissue have been reviewed and genetic counseling and DNA testing performed through full sequencing of the BRCA1 and BRCA2 coding regions and adjacent intronic base pairs.

Of the first 100 women enrolled in the study, 15 (15.0%) had mutations in BRCA1 or BRCA2: 7 in BRCA1 and 8 in BRCA2. No mutations were found among the 6 cases with mucinous tumors. No mutations were found among the 5 cases with borderline tumors; thus, the mutation frequency among invasive tumors was 15.8% (15/95).

These data suggest that 1) the frequency of BRCA1 and BRCA2 mutations among invasive ovarian cancer cases may be higher than previously reported, 2) previous studies may have underestimated the contribution of BRCA2 to ovarian cancer, especially mutations outside the ovarian cancer cluster region (OCCR). Preliminary data regarding risk factors, penetrance, associated cancers and tumor characteristics is being analyzed and will also be presented.